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BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

Application Number: 10/590,808
Filing Date: January 12, 2007
Appellant(s): HOOFT VAN HUIJSDUIJNEN ET AL.

Daniel J Pereira
For Appellant

EXAMINER'S ANSWER

This is in response to the appeal brief filed 7/28/2009 appealing from the Office action mailed 11/14/2008.

(1) Real Party in Interest

A statement identifying by name the real party in interest is contained in the brief.

(2) Related Appeals and Interferences

The examiner is not aware of any related appeals, interferences, or judicial proceedings which will directly affect or be directly affected by or have a bearing on the Board's decision in the pending appeal.

(3) Status of Claims

The statement of the status of claims contained in the brief is correct.

(4) Status of Amendments After Final

No amendment after final has been filed.

(5) Summary of Claimed Subject Matter

The summary of claimed subject matter contained in the brief is correct.

(6) Grounds of Rejection to be Reviewed on Appeal

The appellant's statement of the grounds of rejection to be reviewed on appeal is correct.

The copy of the appealed claims contained in the Appendix to the brief is correct.

(7) Claims Appendix

The copy of the appealed claims contained in the Appendix to the brief is correct.

(8) Evidence Relied Upon

US 2002/0025126 Lui et al. 3-2002

Sowers et al., "Diabetes, Hypertension, and Cardiovascular Disease: An Update" Hypertension 2001:37;1053-1059.

Parissis et al., "Plasma profiles of peripheral monocyte-related inflammatory markers in patients with arterial hyprtension. Correlations with plasma endothelin-1." International Journal of Cardiology 2002:83;13-21.

(9) Grounds of Rejection

The following ground(s) of rejection are applicable to the appealed claims:

Claims 1-16, 20 and 21 are rejected under 35 U.S.C. 103(a) as being unpatentable over Liu et al., (US 2002/0025126) in view of Sowers et al., (Hypertension 2001) and Parissis et al., (International Journal of Cardiology 2002).

Liu et al. teaches the compounds instantly claimed. For example, Liu discloses compounds of Formula I, wherein RI=CH2Ph, R2a and R2b=H and Cy=phenyl substituted with phenyl (see Example 30, at pg. 18). Liu also discloses compounds of Formula I, wherein RI=CH2CH2Ph, R2a and R2b=H and Cy=phenyl substituted with -O-CH2-quinoline (see Example 11, at pg. 15). Liu

also teaches that these compounds are protein tyrosine kinase PTP1B inhibitors useful in treating autoimmune diseases, acute and chronic inflammatory diseases, osteoporosis, obesity, cancer, malignant diseases, and type I and type II diabetes. (See abstract and [0227].)

Liu et al. differs from the instant claims insofar as it does not teach treating coronary obstruction or peripheral vasoconstiction.

Sowers et al. teaches that cardiovascular diseases, including atherosclerosis (coronary obstruction), are a major cause of mortality in persons with diabetes and that hypertension contributes to this high prevalence of cardiovascular disease. (See abstract and HOPE trial at pg. 1055.) The reference also teaches that hypertension and diabetes serve to exacerbate each other (see Id., and pg. 1053, right col., lines 1-3).

Sowers et al. do not teach a compound of formula I.

Parissis et al. teaches that peripheral vasoconstriction is associated with endothelial dysfunction and hypertension, and that patients with hypertension often have a high circulation of endothelin-1, which can result in peripheral vasoconstriction. (See pg. 17, right col. 3rd paragraph to pg. 18, left col. 1st paragraph.)

Parissis et al. do not teach a compound of formula I.

It would have been obvious to a person having ordinary skill in the art at the time of applicant's invention to administer the compounds of Liu for the treatment of coronary obstruction and peripheral vasoconstriction, since they are problems associated with diabetes, as taught by Sowers et al. and Parissis et al. The artisan would reasonably expect success in treating coronary obstruction or peripheral vasoconstriction in a patient by administering the compounds of Liu to diabetic patients since hypertension and diabetes frequently coexist and each pathophysiological disease entity serves to exacerbate the other, as taught by Sowers et al. Thus, in treating diabetes the artisan would reasonably expect a positive effect on hypertension and cardiovascular disease.

(10) Response to Argument

Appellant argues that the combination of the art cited in the rejection does not establish that there would have been a reasonable expectation of success without having had performed the experiments shown in the present specification. However, Sowers et al. states, in regard to diabetes and hypertension, that "each pathophysological disease entity, although independent in their own natural history, serves to exacerbate the other." Thus, by treating one disease, the

exacerbation of the other is prevented or lessened to some degree. In other words, treating diabeties would also treat the hypertension in a patient with diabetes and hypertension. Cardiovascular disease would also be treated since hypertention contributes to a high prevelance of cardiovascular disease in persons with diabetes, as taught in Sowers et al. The claims as written are not necessarily distinquished from Liu since the claims read on treatment of diabetic patients with hypertension, and/or atherosclerosis. The Sowers references strongly suggests a biological link between diabetes, hypertension and cardiovascular disease. It should also be pointed out that the compounds of Liu are useful for treating obesity, also associated with diabetes, hypertension, and cardiovascular disease. Coronary obstruction (e.g. atherosclerosis) and peripheral vasoconstruction result from having cardiovascular disease and hypertension, the artisan would have a reasonable expectation of success in treating these symptoms given the combined teachings of the prior art.

In regard to the data presented in the specification at pages 40 – 41, even if the data supported and unexpected result the instant claims are not commensurate in scope. The instant claims read very broadly in regard to compounds administered, route of administration, concentration and patient population. The data of the specifiction shows *in vitro* incubation of coronary arteries from a

chronic heart failure induced C57Bl6 mouse model with a single compound of Formula (I). The method step is **not** supported here since the compound of Formula (I) was **not** administered to the mouse model. There is also no data showing results for treating peripheral vasocontriction. Since only one compound was tested, there is no reasonable basis for assuming that myriads of compounds not made and thus not tested will share the requisite minimum activity needed to practice the invention.

Appellant argues that Sowers et al. clearly demonstrates that the treatment of one disease does not necessarily positively impacts the other. However, Sowers et al. is a review article and thus it presents a variety of data related to the subject, but the reference more than supports the Examiner's conclusions. To begin, the first line of the Abstract connects the three diseases, "Cardiovascular diseases (CVDs) are the major causes of mortality in persons with diabetes, and many factors, including hypertension, contribute to this high prevalence of CVD." The reference describes a recent, large, prespective cohort study that included 12,550 adults, where "the development of type II diabetes was almost 2.5 times as likely in persons with hypertension than in their normotensive counterparts" (see pg. 1053, left column, second paragraph). The reference goes on to state, "This, in conjunction with ***considerable evidence*** of the increased prevalence of

hypertension in diabetic persons, suggests that these 2 common chronic diseases frequently coexist. Moreover, each pathophysiological disease entity, although independent in its own natural history, serves to exacerbate the other" [emphasis added] (see Id. through right column, lines 1-3). Subsequent to this statement, Sowers et al. makes the statement, referred to by appellant, where patients taking β–blockers had a 28% higher risk of diabetes, but contrasted this data in the following sentences stating, "other randomized prospective trials have not shown an increase in the development of diabetes with β–blocker or low-dose diuretic treatment of hypertension" (see pg. 1053, right column, lines 6-14). Furthermore, the reference discusses diabetic cardiomyopathy, which is a diabetes-related myopathic state characterized by impaired diastolic function.

Appellant argues that Sowers et al. supports the conclusion that antidiabetic treatment would have no direct effect on cardiovascular diseases and teaches away from one skilled in the art to use an antidiabetic treatment to treat a cardiovascular disease. However, this is not true. The quote appellant cited at page 1054 does not support appellant's conclusion. The statement merely suggests that intensive blood pressure reduction was better for reducing the risk of CVD than tight glucose control. This does not mean that tight glucose control did not work or had no direct effect, and it certainly does not teach away.

Appellant also argues that since Sowers et al. taught that diabetic patients required more antihypertensive treatment to achieve goal blood pressure, this does not provide any indication that using an antidiabetic agent would also treat cardiovascular diseases. However, it is unclear how this argument is supported here since that section of Sowers et al., which appellant cites does not discuss treatment with antidiabetic medication. The patients were given blood pressure medication. The study showed that reduction in diastolic pressure form <90 mm Hg to values <85 mm Hg is beneficial in reducing CVD events.

Appellant argues that the only suggestion to do what appellants have done is hindsight. However, It must be recognized that any judgment on obviousness is in a sense necessarily a reconstruction based upon hindsight reasoning. But so long as it takes into account only knowledge which was within the level of ordinary skill at the time the claimed invention was made, and does not include knowledge gleaned only from the applicant's disclosure, such a reconstruction is proper. See *In re McLaughlin*, 443 F.2d 1392, 170 USPQ 209 (CCPA 1971). Here, the rejection is not based on applicant's disclosure but gleaned from the combined teachings of Liu et al., Sowers et al. and Parissis et al.

Appellant distinguishes the Sowers et al. reference by stating obvious differences such as not teaching the compounds of Formula (I), which has been

conceded to by the Examiner, and how ACE inhibitors are completely distinct from PTP1 B. However, the Examiner does not take the position that PTP1 B inhibitors are the equivalent of ACE inhibitors. The function of PTB1 B inhibitors is discussed in Lui et al.

The instant claimed invention is not distinguished from Lui et al. insofar as diabetic patients often have hypertension and cardiovascular disease, as evidenced by Sowers et al. Since Sowers et al. clearly indicates a biological link between diabetes, cardiovascular disease and hypertension, and teaches that one disease exacerbates or contributes to the prevalence of the other, the artisan would have a reasonable expectation of success in treating cardiovascular disease and hypertension, including coronary obstruction and peripheral vasoconstriction, in a diabetic patient by administering a PTP1 B compound of Liu et al.

(11) Related Proceeding(s) Appendix

No decision rendered by a court or the Board is identified by the examiner in the Related Appeals and Interferences section of this examiner's answer.

For the above reasons, it is believed that the rejections should be sustained.

Respectfully submitted,

Walter E. Webb

/Walter E Webb/

Examiner, Art Unit 1612

Conferees:

/Frederick Krass/

Supervisory Patent Examiner, Art Unit 1612

/Ardin Marschel/

Supervisory Patent Examiner, Art Unit 1614